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Guidance for Industry

Effectiveness of Anthelmintics: Specific Recommendations for Feline VICH GL20

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only

This draft guidance is intended to standardize and simplify methods used in the evaluation of new anthelmintics submitted for approval to the European Union, Japan, and the United States.

Comments and suggestions regarding the draft document should be submitted to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the Docket No. 00D-1629.

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EFFECTIVENESS OF ANTHELMINTICS:
SPECIFIC RECOMMENDATIONS FOR FELINE

Recommended for Consultation
at Step 4 of the VICH Process
on 15 June 2000
by the VICH Steering Committee

THIS GUIDANCE HAS BEEN DEVELOPED BY THE APPROPRIATE VICH EXPERT WORKING GROUP AND IS SUBJECT TO CONSULTATION BY THE PARTIES, IN ACCORDANCE WITH THE VICH PROCESS. AT STEP 7 OF THE PROCESS THE FINAL DRAFT WILL BE RECOMMENDED FOR ADOPTION TO THE REGULATORY BODIES OF THE EUROPEAN UNION, JAPAN, AND USA.

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This draft guidance represents the agency's current thinking and does not create or confer any rights for or on any person, and does not operate to bind FDA or the public. An alternative method may be used as long as it satisfies the requirements of the applicable statutes and regulations.

Introduction

The present guidance for feline was developed by the Working Group that was established by the Veterinary International Cooperation on Harmonization (VICH), Anthelmintic Guidances. It should be read in conjunction with the VICH Effectiveness of Anthelmintics: General Recommendations (EAGR) which should be referred to for discussion of broad aspects for providing pivotal data to demonstrate product anthelmintic effectiveness. The present document is structured similarly to the EAGR guidance with the aim of simplicity for readers comparing both documents.

The guidance for feline is part of the EAGR document and the aim is: (1) to be more detailed for certain specific issues for felines not discussed in the EAGR guidance; (2) to highlight differences with the EAGR on effectiveness data recommendations, and (3) to give explanations for disparities with the EAGR guidance.

It is important to note that technical procedures to be followed in the studies are not the aim of this guidance. We recommend that the sponsors refer to the pertinent procedures described in details in other published documents e.g. WAAVP Guidances for Evaluating the Efficacy of Anthelmintics for Dogs and Cats, Veterinary Parasitology 52: 179-202, 1994.

A. General elements

1 – The evaluation of effectiveness data

The evaluation of effectiveness data is based on parasite counts (adults, larvae) in dose determination and dose confirmation studies; egg counts/larval identification is the preferred method to evaluate the effectiveness in field studies.

The controlled test is the most widely accepted of the testing procedures for the evaluation of anthelmintic drug effectiveness. However, the critical test may be appropriate for some intestinal species of parasites. Adequate parasite infection should be defined in the protocol according to regional prevalence or historic and/or statistical data.

2 – Use of natural or induced infections

Dose determination studies should be conducted using induced infections with either laboratory or recent field isolates.

Dose confirmation studies should be conducted using naturally or artificially infected animals. Generally, at least one study should be conducted in naturally infected animals for each parasite claimed on the labeling. *Echinococcus multilocularis* and *Dirofilaria* spp. testing may be conducted using only animals which harbour induced infections due to public health considerations for echinococcosis and the complexity of the claims for heartworm. For the following helminths, induced infections may also be the only method to determine effectiveness of the product because of the difficulties in obtaining a sufficient number of infected animals:

Capillaria aerophila, Physaloptera spp.*, Crenosoma vulpis.* For claims against larval stages, only studies with induced infections should be used.

The history of the parasite cultures used in the induced infection studies should be included in the final report.

3 – Number of infective parasitic forms recommended for induced infections.

The number to be used is approximate and will depend on the isolate that is used. The final number of larvae used in the infection should be included in the final report. Table 1 shows the range of numbers recommended for common helminths.

Table 1- Numbers of infective stages used to produce adequate infections of common helminths in cats for anthelmintic evaluation

Parasites	**Range of eggs/larvae**
Small Intestine:	
Toxocara cati	100 - 500
Toxascaris leonina	200 - 3,000
Ancylostoma tubaeforme	100 - 300
Ancylostoma braziliense	100 - 300
Strongyloides stercolaris	1,000 - 5,000
Echinococcus multilocularis	20,000 - 40,000
Taenia taeniaeformis	5 - 15
Dipylidium caninum	15 - 30
Large Intestine	
Trichuris campanula	100 - 500
Heart	
Dirofilaria immitis	30 - 100*

* For adulticidal or microfilarial testing 5 to 15 pairs of adult worms can be transplanted

4 – Recommendations for the calculation of effectiveness

4.1. Criteria to grant a claim:

To be granted a claim the following pivotal data should be included:

a) Two dose confirmation studies conducted with a minimum of 6 adequately infected non-medicated animals (control group) and 6 adequately infected medicated animals (treated group);

b) The differences in parasite counts between treated and control should be statistically significant ($p<0.05$);

c) Effectiveness should be 90% or higher calculated using transformed (geometric means) data. For *E. multilocularis* and *D. immitis* with public animal welfare/clinical implications, respectively, higher efficacy standards (i.e. up to 100%) may be applied. The regulatory authority of the region in which the product is intended to be registered should be consulted;

d) The infection of the animals in the study will be deemed adequate based on historical, parasitological and/or statistical criteria;

e) Field effectiveness against helminths will be evaluated examining for the presence or absence of parasitic elements in fecal material or blood. *Echinococcus multilocularis* claim does not require field studies due to public health concerns**.**

4.2 Number of animals (dose determination and dose confirmation trials)

The minimum number of animals used per experimental group is a critical point. Although the number of animals will depend on the ability to process the data statistically according to the adequate statistical analysis it has been recommended, to achieve harmonization, that the inclusion of at least 6 animals in each experimental group is a minimum.

In cases where there are several studies, none of which have 6 adequately infected animals in the control group (for example, important rare parasites), the results obtained could be pooled to accumulate 12 animals in the studies; and statistical significance calculated. If the difference is significant ($p<0.05$), effectiveness may be calculated and if the infection is deemed adequate, the claim may be granted. Sampling techniques and estimation of worm burden should be similar among laboratories involved in the studies to allow adequate and meaningful extrapolation of the results to the population.

4.3 Adequacy of infection

A universal definition of adequacy of infection cannot be formulated because of the diversity of genera, species, and strains of helminths subject to evaluation. Furthermore, each strain under test may have unique characteristics of infectivity and pathogenicity. However, in the development of study protocols the adequacy of infection should be addressed, especially in terms of the statistical, parasitological, and clinical relevance of the infection level in individual control animals, as well as the number of control animals.

The level of infection, and it's distribution, among control animals should be adequate to permit the appropriate standards of effectiveness to be met with acceptable statistical and biological certitude/confidence. Multiple infections are acceptable; however, each helminth species should reach acceptable minimums of infection.

In cases where the regulatory authorities and sponsor cannot agree on a minimum adequate number, the decision will be made when the final report is submitted based on historical data, literature review, or expert testimony. Generally, the minimal number of nematodes in cats considered to be adequate is in the range of 5 to 20. Higher counts are to be expected with *A. tubaeforme*.

4.4 Label claims

A claim for effectiveness against life stages of each parasite should refer to each stage in the case of natural infections, or age in days in the case of induced infection. Table 2 is provided as a guide for the recommended time of treatment of induced infections.

With the majority of parasites approximately 7 days is a sufficient time period from the termination of treatment until the test animals are necropsied. The following parasites are the exception to the above general recommendation:

- *Physaloptera* spp*., C. aerophila, E. multilocularis, Taenia taeniaeformis*, *D. caninum*: 10 to 14 days
- *C. vulpis:* 14 days
- *D. immitis:* varied by trial design

Table 2 – Recommended time of treatment after infection

Parasite	Adult Stages	Developing Stages
S. stercoralis	5 to 9 days	
T. campanula	84 days	
T. tubaeforme	>21 days	6 to 8 days*
A. braziliense	>21 days	6 to 8 days
T. cati	60 days	3 to 5 days (migrating), 28 days (intestinal); for breeding females, treat at 7 to 14 days prior to parturition
T. leonina	70 days	35 days
D. immitis	180 days	2 days (L3), 20 to 40 days (L4) 70 to 120 days (L5), 220 days (microfilaria)
E. multilocularis	>18 days	
T. taeniaeformis	>35 days	
D. caninum	>28 days	

*For somatic larvae, treat within 2 days prior to parturition

5 - Treatment procedures

The method of administration (oral, chewable products, parenteral, and topical) and extent of activity of the product will influence the protocol design. It is advisable to consider the weather and animal relationship and bathing with regard to effectiveness of topical formulations.

For oral formulations, palatability studies should always be included in the evaluation of the effectiveness of the product. For products administered topically, the impact of weather (e.g. rainfall, UV light), bathing and coat length should be included in the evaluation of the effectiveness of the product.

6 - Animal selection, allocation and handling

Approximately six-month-old cats are generally suitable for controlled studies, however, older and younger animals can also be used and the following exceptions should be taken into account:

- *S. stercoralis*: less than 6 months
- *A. braziliense, A. tubaeforme:* 6 to 16 weeks
- *T. cati, T. leonina:* 4 to 16 weeks
- *D. caninum:* 3 months or older

Naturally infected animals are selected based on egg output or expelled proglottids in gastrointestinal parasites, and parasitological and/or immunological methods for *D. immitis*. They should be assigned to the each group and replicated using an adequate method that should be described in the final report. Replications should cover each factor that may have an impact on the final evaluation of the effectiveness of the formulation. Animal housing, feeding, and care should follow strict recommendations of welfare for cats. Animals should be acclimated for at least 7 days to the experimental facilities and personnel.

B. Specific evaluation studies

1 - Dose determination studies

No species specific recommendations.

2 - Dose confirmation studies

In general, a minimum of 2 dose confirmation studies should be included for each parasite claim, adult and larval stages. However, due to the unique relationship between people and cats and the difficulties in obtaining suitable infected animals, there may be instances where there is justification to reduce the dose confirmation recommendations. In such a case, field effectiveness data should provide proof for effectiveness. For additional descriptions of the procedures refer to EAGR.

3 - Field effectiveness studies

Field (clinical) studies should not be conducted with cats infected with *E. multilocularis* and *D. immitis.*

4 - Persistency effectiveness studies

Due to the differing biology of helminths in cats and the lack of experience with persistent effectiveness claims for these parasites, no recommendations can be provided.